HuGE Fact Sheet

Mismatch Repair Genes hMLH1 and hMSH2 and Colorectal Cancer

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Gene

The human mutL homologue *hMLH1* is located at chromosome 3p21-23, and the gene product is a component of the DNA mismatch repair pathway. The gene product of the mutS homologue *hMSH2* is another component of this pathway, and the gene is located at chromosome 2p21.

Prevalence Of Gene Variants

Thus far more than 200 different variants have been characterized in each of the *hMLH1* and *hMSH2* mismatch repair genes. Variants in *hMLH1* and *hMSH2* are highly heterogeneous, and classification by pathogenicity is subject to interpretation based on predicted effect on protein, segregation with disease, and presence in control subjects where such data are available. Classification of variants by the authors of the accompanying HuGE review revealed that 259 pathogenic mutations and 45 polymorphisms have been reported in *hMLH1*, while 191 pathogenic mutations and 55 polymorphisms have been identified in *hMSH2* (1) . However, these figures are affected by substantial publication bias and the actual number of polymorphic variants is likely to be much higher. Because of the costs involved in conducting thorough mutation analysis of these genes, data on prevalence of gene variants are largely confined to colorectal cancer cases. The only published estimate of the prevalence of mutations in the population estimated that 1 in 3139 (95% CI = 1:1247, 1:7626) members of the population of Scotland carried a pathogenic mutation (2) . Founder effects, in which many mutation carriers can be traced to a common ancestor, are known to exist in some populations, notably that of Finland. Otherwise, available data provide no evidence for ethnic or population variation.

Disease Burden

Colorectal cancer is a major public health problem throughout the world. Several dietary and environmental risk factors have been identified, and there is also a significant genetic contribution to the aetiology of the condition. A small proportion of all colorectal cancer cases cluster in families, or occur at an unusually young age, and are therefore thought to have a largely genetic basis. Pathogenic mutations in mismatch repair genes, particularly *hMLH1* and *hMSH2*, have most often been described in association with such cases. The actual proportion of colorectal cancer cases attributable to such mutations has not been determined but is likely to be around 1%. Evidence of a causal role for variants of *hMLH1* and *hMSH2* in a subset of colorectal cancer cases comes from both epidemiological and molecular studies. However, conventional epidemiological evidence is lacking because of the expense of mutation analysis in controls. The most compelling evidence comes from studies demonstrating that mutation carriers are at a significantly increased risk of developing colorectal cancer compared with the general population (3,4,5) . Estimates of lifetime risks from these studies suggest that the penetrance of pathogenic mutations in *hMLH1* and *hMSH2* that are related to colorectal cancer is around 80% in males and 40% in females.

Interactions

Currently limited evidence exists for interactions between mismatch repair gene mutations and other known risk factors for colorectal cancer. Further exploration is merited for potential interactions with genetic risk factors such as N-acetyltransferase and p53 and with environmental risk factors such as smoking.

Laboratory Tests
A wide variety of techniques and combinations of techniques have been employed to identify variations in *hMLH1* and *hMSH2*. These include genomic sequencing, with an estimated sensitivity of 80%, and the in vitro synthesized protein assay (IVSP), with a sensitivity of around 69% (6). Other techniques, such as denaturing gradient gel electrophoresis (DGGE) and single-strand conformational polymorphism (SSCP), rely on alterations in DNA structure to indicate the presence of mutations. Sensitivity is comparable to that of IVSP.

Population Testing
Information regarding the prevalence and penetrance of mismatch repair gene mutations as well as evidence of effective intervention strategies for mutation carriers are currently insufficient to recommend population testing outside of the research context. However, testing of early-onset colorectal cancer cases and individuals with a significant family history of colorectal cancer can be justified. Such targeted testing enables additional mutation carriers to be identified by "cascade" screening of relatives.

References

1. Mitchell RJ et al. Mismatch repair genes hMLH1 and hMSH2 and colorectal cancer: a HuGE review. *Am J Epidemiol* 2002;156:885-902.
2. Dunlop MG et al. Population carrier frequency of hMSH2 and hMLH1 mutations. *Br J Cancer* 2000;83:1643-5.
3. Aarnio M et al. Cancer risk in mutation carriers of DNA-mismatch-repair genes. *Int J Cancer* 1999;81:214-8.
4. Dunlop MG et al. Cancer risk associated with germline DNA mismatch repair gene mutations. *Hum Mol Genet* 1997;6:105-10.
5. Vasen HF et al. Cancer risk in families with hereditary nonpolyposis colorectal cancer diagnosed by mutation analysis. *Gastroenterology* 1996;110:1020-7.
6. Farrington SM et al. Systematic analysis of hMSH2 and hMLH1 in young colon cancer patients and controls. *Am J Hum Genet* 1998;63:749-59.

Web Sites

Genetic Information and Databases:

- International Collaborative Group, Hereditary Non-Polyposis Colorectal Cancer
- Online Mendelian Inheritance in Man

Patient Education and Support:

- World Cancer Research Fund
- International Union Against Cancer